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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,243	01/22/2002	Maurice Israel	033532-001	8007

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EXAMINER
MCINTOSH III, TRAVISS C

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	10/051,243	ISRAEL ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Preliminary Amendment/Election

The Amendment filed June 18, 2003 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

The specification has been amended to correct typographical errors of Formula I as indicated.

Claims 1, 5, 7, and 9 have been amended.

It is noted by the examiner, that there appears to be a typographical error in Formula II as well as there was for formula I. Based on WO 01/05404, the published document for applicants priority document PCT/FR00/02120, formula II appears to have the same double bonds as formula I does in the bicyclic naphthyl core. The examiner has interpreted this as a typographical error in the expectation that applicants will amend formula II in the specification and the claims as they have done so with formula I.

Election/Restrictions

Applicant's election with traverse of group IV in Paper No. 6 is acknowledged. The traversal is on the ground(s) that a search for one group would almost necessarily include a search directed to the subject matter of the other claims. This is not found persuasive because a reference rendering one of the groups obvious would not necessarily render the other obvious,

and a search for one group would not necessarily entail a search for the others. The groups are directed at: 1) treating/preventing glutamate-evoked cytotoxicity; 2) modulating (increasing or decreasing) the release of glutamate; 3) inhibiting the release of glutamate; and 4) treating/preventing disease associated with excessive release of glutamate. As such, a reference showing the claimed compounds increase glutamate release would not render the other groups obvious.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

It is noted, that the species election set forth in the Office Action dated March 21, 2003 is hereby being withdrawn, and both derivatives of formula I and formula II (sugars and non-sugars) will be examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of conditions associated with the excessive release of glutamate by administering naftazone or its glucuronide derivative, does not reasonably provide

enablement for prevention of conditions associated with the excessive release of glutamate by administering the generic compounds I or II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant disclosure is not seen to be sufficient to enable the use of the generic compounds of formulas I or II to **prevent any condition associated with the excessive release of glutamate** without undue experimentation

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to a method of preventing or treating conditions associated with the excessive release of glutamate by administering the beta-naphthoquinones of formulas I or II, and specifically naftazone or its glucuronide derivative.

The state of the prior art

Beta-naphthoquinones are known in the art to be used as vasoprotective drugs. Glutamate is known in the art to be the main excitatory neurotransmitter in the nervous system. Glutamate cytotoxicity is known to be associated with many diseases neurological diseases like Alzheimer or Parkinson's disease (as seen in Rosenberg US Patent 5,158,976). At present, there are no known agents capable of preventing all diseases associated with excessive release of glutamate, such as Alzheimer's disease.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agent, which is naftazone or its glucuronide derivative, indeed has efficacy in treating certain conditions associated with excessive glutamate release, however the art is silent with regard to the predictability of effectively preventing the development of any condition associated with excessive glutamate release.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been

provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy of prevention instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are drawn to the following examples:

Example 1: Three groups of rats were set: I a control group (n=8), II treated with 10 mg/kg/day of naftazone (n=5), and III treated with 100 mg/kg/day of naftazone (n=5). The cerebrospinal fluid of the rats was then collected and glutamate levels were determined.

Example 2: Naftazone and its glucuronide derivative were tested to determine the spontaneous release of glutamate from synaptosomes of mouse brains.

There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that a healthy individual would never become afflicted with any disease or condition which is associated with the excessive release of glutamate if subjected to the instantly claimed therapy.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of the compounds of general formulas I and II to prevent the development of any disease or condition associated with the excessive release of glutamate without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Reasonable guidance with respect to preventing any condition relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of the condition. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the prevention of the disease is the essence of verification of a valid preventive agent. Moreover, a single species (naftazone or its glucuronide derivative) is seldom, if ever, sufficient to support a generic claim. See ***In re Shokal, 242 F.2d 771, 13 USPQ 283, 285 (CCPA 1957).***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10, which depends from claim 9, is confusing wherein the claim limits "said derivative" to 3 compounds, yet claim 9 provides a method of treating a condition associated with excessive glutamate release by administering at least one beta-naphthoquinone derivative selected from (i) compounds having formula I, (ii) glucuronide derivatives having formula II, or

(iii) addition salts thereof. Does applicant intend the derivative of claim 10 to limit the beta-naphthoquinone derivative, or the glucuronide derivative? Clarity is respectfully requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 9-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Mattei et al. ("Naftazone reduces glutamate cerebro spinal fluid levels in rats and glutamate release from mouse cerebellum synoptosomes", Neuroscience Letters, vol. 271, pp. 183-186, 1999).

The claims are drawn to treating conditions associated with the excessive release of glutamate by administering naftazone or its glucuronide derivative.

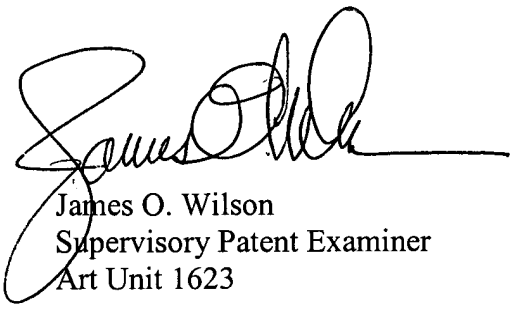
Mattei et al. disclose that naftazone decreases glutamate levels in cerebrospinal fluid and that naftazone or its glucuronide derivative also reduced the spontaneous and high K^+-evoked glutamate release from cerebellum synaptosomes wherein the naftazone and its glucuronide derivative are likely to decrease glutamate levels in the cerebrospinal fluid through their inhibitory actions on glutamate release.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
September 23, 2003